Genetics of systemic autoimmunity and glomerulonephritis in mouse models of lupus

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Introduction

Systemic lupus erythematosus (SLE) is a prototypic antibody-mediated systemic autoimmune disease characterized by a high female predominance (90%), a broad spectrum of autoantibodies that typically includes reactivity to nuclear antigens, and multisystem pathology. There is no single discriminatory test, and clinical manifestations are highly variable among patients. There remains significant morbidity for most patients and increased mortality especially for those with renal or CNS involvement, despite the use of powerful immunosuppressive intervention.

Although the cause of SLE is not known, there is substantial evidence pointing to a combination of underlying genetic susceptibility. Definition of the genetic basis for lupus would provide the means to not only identify predisposed individuals, but to develop therapeutics directed at correcting susceptibility gene defects or antagonists to the gene products critical for disease pathogenesis. Research in this area, however, has been hampered by the complex multifactorial inheritance and heterogeneity of SLE. Nonetheless, substantial progress in methods to identify genes responsible for polygenic disorders has been made over the past several years, particularly for animal models. Such models, involving genetically homogeneous animals, are particularly useful in studies of complex inheritance such as lupus because of the ability to control for genetic and environmental variations. Moreover, genetic manipulation can readily be performed to test the function of specific loci and genes. We, and others, are applying these strategies to lupus-prone mouse strains to identify and define the contributions of susceptibility genes, as well as to dissect the function of known genes in the pathogenesis of the disease.

Loci predisposing to systemic autoimmunity in lupus-prone mouse strains

Thus far, only a handful of susceptibility genes have been identified in mice with spontaneous SLE. These include the MHC, the Fas (lpr and lprcg mutations) and related Fas ligand (gld mutation) genes, and the Y chromosome associated with accelerated autoimmunity (Yaa) gene in BXSB male mice that has not yet been cloned [1]. In all instances, however, the development of lupus-like disease requires the presence of other, yet undefined, lupus-predisposing background genes that appear to shape the severity, autoantibody profiles and types of end-organ disease.

NZ susceptibility loci

Our initial genome-wide linkage study of (NZB×NZW)F2 mice revealed eight loci designated Lbw1-8, that were located on chromosomes 17, 4, 5, 6, 7, 18, 1, and 11, respectively, and linked to one or more component phenotypes, including mortality, glomerulonephritis (GN), IgG anti-chromatin autoantibody production, and splenomegaly [2]. Lbw1 was linked to mortality, GN and anti-chromatin autoantibodies critical for disease pathogenesis. Research in this area, however, has been hampered by the complex multifactorial inheritance and heterogeneity of SLE. Nonetheless, substantial progress in methods to identify genes responsible for polygenic disorders has been made over the past several years, particularly for animal models. Such models, involving genetically homogeneous animals, are particularly useful in studies of complex inheritance such as lupus because of the ability to control for genetic and environmental variations. Moreover, genetic manipulation can readily be performed to test the function of specific loci and genes. We, and others, are applying these strategies to lupus-prone mouse strains to identify and define the contributions of susceptibility genes, as well as to dissect the function of known genes in the pathogenesis of the disease.

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chromosome 1 overlaps with Sle1 [5] and Nba2 [10]. Lbw7 and Nba2 are inherited from the NZB strain and likely represent the same locus, whereas Sle1 is from the NZW genome and, therefore, different. Interestingly, both the NZB (Lbw7 and Nba2) and NZW (Sle1) loci are linked to anti-chromatin production, however, the NZB locus is also linked to the production of autoantibodies to the endogenous retroviral glycoprotein, gp70 [11]. Inheritance of autoimmune traits in the (NZB×NZW)F2 mice appeared to be dependent on both the number and specific combinations of susceptibility alleles (multiplicative epistasis model), which has been supported by subsequent studies. It was also noted that some loci predisposing to mortality were not linked to autoantibody production, or in some cases to GN. This suggested that NZ genes may contribute to systemic autoimmunity not only by promoting loss of tolerance and autoantibodies, but also by influencing kidney disease pathogenesis at later stages.

To further define the role of the non-MHC dominant susceptibility loci (Lbw2, Lbw5, and Lbw7) in lupus-like disease, reciprocal interval-specific congenic mice are being studied. This strategy allows examination of Lbw loci in both parental strain backgrounds and in the (NZB×NZW)F1 hybrid, the model considered to most closely resemble human SLE. Furthermore, the effect of replacing the susceptible chromosomal interval with the non-susceptible interval on the severity and manifestations of disease would provide an indication of the potential benefit of intervention. Importantly, BWF1 mice lacking the NZB Lbw2 interval had a significant improvement in 1-year survival compared with wild-type F1 hybrids increasing from approximately 10–50%. From a therapeutic standpoint, this clearly shows that correction of a single non-MHC predisposing locus can have a dramatic effect on overall course of the disease despite the other remaining genetic contributions to disease.

Lupus susceptibility loci in (MRL-Faslpr×B6-Faslpr)F2 mice

Defects in the apoptosis-promoting Fas/FasL receptor-ligand pair of cell surface molecules, in lpr and gld mice, respectively, are associated with massive accumulations of CD4−CD8− (double negative) T cells, hypergammaglobulinaemia, autoantibodies, and a spectrum of autoimmune manifestations that resemble lupus, such as systemic vasculitis, arthritis, and Sjogren syndrome [1]. Similar findings have also been observed in humans with the rare autoimmune lymphoproliferation syndrome (ALPS or Canale-Smith syndrome) caused by mutations in genes related to the Fas apoptosis pathway (Fas, FasL, caspase 10) [12]. The mechanism by which Fas/Fasl deficiency leads to these abnormalities appears primarily due to defective activation-induced cell death (AICD) of B and T cells in the periphery and the expansion of self-reactive cells [1].

Although defects in Fas-mediated apoptosis strongly predispose to systemic autoimmunity, full expression of lupus disease clearly requires the presence of additional susceptibility genes. Thus, disease in non-autoimmune C57BL/6 mice homozygous for the Faslpr mutation is manifested by the late-onset production of autoantibodies, including both anti-nuclear and rheumatoid factor, but no further disease progression. In contrast, the lupus-predisposed MRL strain with either the Faslpr or Faslgl mutations develops not only early onset autoantibodies, but severe GN, vasculitis, and arthritis that results in a 50% mortality around 5–6 months of age.

To define the MRL background susceptibility genes, we examined a panel of (MRL×C57BL/6)F2-Faslpr intercross mice for quantitative trait loci (QTL) to lymphoproliferation, IgG anti-dsDNA antibody production, and GN [13]. Four major loci were initially identified, designated Lmb1-4, on chromosomes 4, 5, 7, and 10, respectively. All four QTL were linked to lymphoproliferation, three were also linked to anti-dsDNA antibodies (Lmb1-3) and one was also linked to GN (Lmb4). As expected, the susceptible QTL for most of these loci were derived from the MRL strain (Lmb2-4); however, one of the QTL (Lmb1) was linked to the non-autoimmune C57BL/6 strain. These findings raise the possibility that mice (and humans) considered non-autoimmune may also have susceptibility alleles, but that the number and specific combination of susceptibility alleles may not be sufficient to induce overt disease.

Interestingly, although anti-dsDNA autoantibodies are considered pathogenic for GN, this trait did not map to Lmb4, the only locus significantly linked to GN. This suggested that Lmb4 predisposed to a later stage of disease pathogenesis than autoantibody production, or possibly to the production of other pathogenic autoantibody specificities.

Lupus susceptibility loci in (BXSB×NZW)F2 mice

Studies of F1 hybrids have shown complementation among NZB, NZW, and BXSB lupus-prone strains in both sexes regardless of the specific combination. The accelerated disease in males is largely due to the Yaa gene on the BXSB Y chromosome, whereas, the disease in females comes only from the contribution of dominant autosomal genes. As major complementing loci for the (NZB×NZW)F2 cross have been defined, we analysed female (BXSB×NZW)F2 mice to identify their complementing loci and to compare the results from the two crosses. In preliminary work, seven loci were identified on six chromosomes. A chromosome 1 locus was linked to anti-chromatin Ab and arteritis, a chromosome 4 locus to anti-chromatin Ab, a chromosome 5 locus to survival, a chromosome 6 locus to GN...
and arteritis, and chromosome 7 locus to splenomegaly, a proximal chromosome 17 (MHC region) locus to all traits except arteritis, and a more distal chromosome 17 locus to arteritis. Two non-MHC loci were inherited from BXSB, but the others were derived from the NZW.

Conclusions

In summarizing these mapping studies, the most striking finding is the number of diverse loci that have been identified in studies using relatively small numbers of animals in each cross. Small sample sizes tend to randomly exaggerate the effects of certain loci and reduce the significance of others. A large cross would help to clarify many of the uncertainties regarding the number, significance, and relationships of loci and component phenotypes. The findings have, nonetheless, provided a crude picture of the genetic susceptibility to lupus and some provocative hints as to how genes may contribute to disease pathogenesis. Importantly, the fact that component phenotypes contributing to lupus pathogenesis can be mapped and expressed in interval-specific congenic mice, will make it possible to identify and define the contributions of the multiple genes and to dissect their interactions.

References

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